REMARKS

Claims 1-70 were pending in this application. Claims 7, 8, 12-17, 19-21, 25-27, 32-42, 53, 55-57, 61, and 63-70 have been withdrawn from consideration as non-elected subject matter. Applicants have canceled clams 1-70 without prejudice. Applicants reserve the right to pursue the subject matter of the withdrawn/canceled claims in a related application(s), without relinquishing the scope of the claimed subject matter. Applicants have added new claims 71-76 for consideration. Support for the new claims and amendments can be found throughout the specification including pg 4-ln. 19-34, pg 5-whole page, pg 6-whole page, pg 13-ln 24-36, pg 48-ln 27-36, and pg 113-ln 17-27.

Applicants have amended the specification to remove the term "etaracizumab" as requested by the Examiner. Applicants respectfully assert that no new matter has been added and request entry of said amendments.

The Examiner's First Rejection Under 35 U.S.C. § 112 2nd Paragraph, Should Be Withdrawn:

The Examiner has rejected claims 1-6, 9-11, 18, 22-24, 28-31, 43-52, 54, 58-60 and 62 based on U.S.C. § 112 2nd paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically the Examiner states that there is an overlap between the recited "immunomodulatory agents" and "immunosuppressive agents" and furthermore, the term "immunomodulatory" is relative in nature. Applicants respectfully disagree. Applicants submit that the rejection of claims 1-6, 9-11, 18, 22-24, 28-31, 43-52, 54, 58-60 and 62 is now moot due to the cancellation of claims 1-70. Based on the cancellations above, Applicants respectfully request this rejection be withdrawn and not applied to the new claims.

The Examiner's Second Rejection Under 35 U.S.C. § 112 2nd Paragraph, Should Be Withdrawn:

The Examiner has rejected claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 as being allegedly indefinite in the recitation of "VITAXIN™",

"REMICADE™", "etaracizumab", and "infliximab". The Examiner states that aforementioned terms, as the sole means of identifying the claimed antibodies renders the claims indefinite because these are merely laboratory designations or non-proprietary names which do not clearly define the claimed products. Applicants respectfully disagree. However, solely in an effort to expedite prosecution, Applicants have amended the claim set to remove the terms "VITAXIN™", "REMICADE™" and "etaracizumab". Applicants respectfully point out that the term "infliximab" is cited throughout the specification in reference to "REMICADE™" (see pg. 13 ln. 28, pg. 15 ln. 16, pg. 18, ln. 33, pg. 113 ln. 25-26, pg. 113 ln. 23-24 of the instant specification for examples). In addition, Applicants submit that the enclosed product information from the Physicians Desk Reference, 55th edition, 2001 (a copy of which is enclosed as Exhibit A) also defines the term "infliximab" as the generic name for "REMICADE™". Applicants respectfully assert that one of skill in the art would have been able to ascertain the antibody encompassed by the term "infliximab" in light of the disclosure in the specification and/or the disclosure in Physicians Desk Reference. Applicants also submit that the rejection based on claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 is now moot due to the cancellation of claims 1-70. Based on the claim amendments, cancellations and arguments above, Applicants respectfully request this rejection be withdrawn and not applied to the new claims.

The Examiner's Third Rejection Under 35 U.S.C. § 112 2nd Paragraph, Should Be Withdrawn:

The Examiner further maintains that the recitation of "VITAXIN™", "REMICADE™", "etaracizumab" and "infliximab" are indefinite as the formula or characteristics of the product may change over time. Applicants respectfully disagree. However, solely in an effort to expedite prosecution, Applicants have amended the claim set to remove the terms "VITAXIN™", "REMICADE™" and "etaracizumab". With respect to the term "infliximab" Applicants assert that the disclosure submitted as Exhibit A coupled with the reasons stated above support the fact that "infliximab" is the USAN approved generic name describing a defined commercial product and is not a TRADEMARK or a trade name. Applicants also point out, as discussed above;

infliximab was understood in the art at the time of the invention. Applicants also submit that the rejection based on claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 is now moot due to the cancellation of claims 1-70. Based on the claim amendments, cancellations and arguments above, Applicants respectfully request this rejection be withdrawn and not applied to the new claims.

The Examiner's Fourth Rejection Under 35 U.S.C. § 112 1st Paragraph, Should Be Withdrawn:

The Examiner has rejected claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 are rejected under 35 U.S.C. §112 1st paragraph as lacking written description of the claimed invention. Specifically, the Examiner states that the specification as originally filed does not provide support for the terms "etaracizumab" and "infliximab". Applicants respectfully disagree. However, solely in an effort to expedite prosecution, Applicants have amended the claim set to remove the term "etaracizumab". With respect to the term "infliximab", Applicants submit that specification as filed provides ample support for the term "infliximab" (see pg. 13 ln. 28, pg. 15 ln. 16, pg. 18, ln. 33, pg. 113 ln. 25-26, pg. 113 ln. 23-24 of the instant specification for examples). Applicants submit that the enclosed product information from the Physicians Desk Reference, 55th edition, 2001 (Exhibit A) also clearly defines the term "infliximab" as the generic name for "REMICADE™". Applicants also submit that the rejection based on claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 is now moot due to the cancellation of claims 1-70. Based on the claim amendments, cancellations and arguments above, Applicants respectfully request this rejection be withdrawn and not applied to the new claims.

The Examiner's Fifth Rejection Under 35 U.S.C. § 112 1st Paragraph, Should Be Withdrawn:

The Examiner has rejected claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 are rejected under 35 U.S.C. §112 1st paragraph as containing subject matter which was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Specifically the Examiner states that the

"VITAXIN™", "REMICADE™", "etaracizumab", and "infliximab" antibodies are required to practice the invention and as required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Applicants respectfully disagree. In an effort to expedite prosecution, Applicants have amended the claim set to remove the terms "VITAXIN™", "REMICADE™" and "etaracizumab". Applicants respectfully submit that the antibody "infliximab" was both known and readily available to the public as evidenced by both the disclosures in the instant specification (see pg. 13 ln. 28, pg. 15 ln. 16, pg. 18, ln. 33, pg. 113 ln. 25-26, pg. 113 ln. 23-24 of the instant specification for examples) and the submitted product information from the Physicians Desk Reference, 55th edition, 2001 (Exhibit A). Applicants also submit that any additional claimed antibodies of the invention are obtainable by a repeatable method as described in the instant specification and incorporated references therefore satisfying the requirements of 35 U.S.C. §112 1st paragraph. Applicants also submit that the rejection based on claims 2, 4, 6, 9-11, 18, 22-24, 28-31, 43-54, 58-60 and 62 is now moot due to the cancellation of claims 1-70. Based on the claim amendments, cancellations and arguments above, Applicants respectfully request this rejection be withdrawn and not applied to the new claims.

The Examiner's Rejection Under 35 U.S.C. § 103(a), Should Be Withdrawn:

The Examiner has rejected claims 1-6, 9-11, 18, 22-24, 28-31, 43-52, 54 and 58-62 under 35 U.S.C. § 103(a) as being unpatenable over Feldman et al. (U.S. Patent No. 6,270,755 hereinafter "Feldman") in view of Huse (U.S. Patent No. 6,596,850, hereinafter "Huse"), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (pg 416-423) and Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996 (pg 451-456). Applicants respectfully disagree with traverse to this rejection for the following reasons.

The MPEP (8th ed. Aug 2001), 2143 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

> art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Applicants respectfully submit that the cited references do not teach nor suggest, alone or in combination, all the limitations of the claimed invention. In addition there is no motivation in the primary references to modify or to combine specific treatment regimes including the specific combinations of the claimed invention. However, solely in an effort to expedite prosecution and not acquiescing to the Examiner's rejection, Applicants have canceled claims 1-6, 9-11, 18, 22-24, 28-31, 43-52, 54 and 58-62. Applicants submit new claims 71-76 and request that the rejection not be applied to the new claims.

Teachings of the Cited References

Feldman

Feldman teaches the use of anti-TNF-α antagonists, including cA2 (REMICADE™, see columns 7-16) in combination with methotrexate (see columns 18-20) in various dosing scenarios in order to maintain the reduction or elimination of symptoms associated with a particular TNF-α mediated disease (see columns 18-20).

Applicants reaffirm, that Feldman is limited in its scope as it only teaches the combination of TNF-α antagonist therapy with methotrexate to alleviate TNF-α mediated diseases. Feldman also does not teach nor suggest that one could target integrins, through an antagonist to alleviate the signs of a TNF-α mediated disease (see abstract, page 4, ln 19-36, page 5 ln 1-33 of the instant specification). Feldman is also deficient by containing no teaching of targeting adhesion, migration, or angiogenesis, known physiological properties influenced by $\alpha_v\beta_3$ integrins, in order to treat a TNF-α mediated disease. Feldman also does not contain any teaching or suggestion of combining $\alpha_v\beta_3$ specific antibodies or antigen binding fragments thereof and infliximab or antigen binding fragments thereof in a method of treating rheumatoid arthritis as claimed by the current invention.

Huse

Huse does not cure the above deficiencies of Feldman. Huse does not teach the specific combination of therapies, namely, the $\alpha_v\beta_3$ specific antibody or an antigen binding fragment thereof and infliximab or an antigen binding fragment thereof in a method of treating rheumatoid arthritis, as claimed by the current invention.

The Secondary References

Again, Applicants respectfully affirm that the secondary references cited by the Examiner (The Merck Manual pages 416-423, and Strom et al. pages 451-456) when combined with Feldman and Huse also fail to obviate the present invention. These references relate to conventional immunosuppressive therapy, including non-steroidal inflammatory drugs, salicylates, methotrexate and corticosteroids (see Merck pages 419-423, Strom et al. pages 451-456), but do not point the skilled artisan to the particular claimed combinations. Furthermore, Strom et al. teaches immunosuppressive therapy during organ transplantation, a condition independent of the teaching of the instant specification and of the claimed invention. As such, the secondary references add little to the teachings of Feldman and Huse.

The Combination of References

None of the cited references teach or suggest the claimed $\alpha_v\beta_3$ integrin specific antibody with the recited CDR sequences or antigen binding fragment thereof in combination with infliximab or an antigen binding fragment thereof in a method of treating rheumatoid arthritis as presently claimed. Indeed, the Examiner acknowledges that "Feldman differs from the claimed methods by not describing all of the current methods of treating rheumatoid arthritis as referenced herein by the Merck Manual, as well as the use of alphavbeta3-specific antibodies in the treatment of rheumatoid arthritis" (see page 7, 4th paragraph of the detailed non-final office action). Applicants respectfully assert that it would not have been obvious to one skilled in the art based upon the cited references to identify targeting the $\alpha_v\beta_3$ integrin with specific antibodies in combination with infliximab to treat rheumatoid arthritis as presently claimed.

In further support of this rejection, the Examiner has also cited the MPEP(8th ed. Aug 2001), 2144.06 which states:

> It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

The Applicants respectfully assert that the claimed invention does not include a combination of two compositions taught in the prior art useful for the same purpose to form a third. The claimed invention incorporates two distinct targets for therapeutic access for the treatment of rheumatoid arthritis (RA). The $\alpha_v\beta_3$ integrin has been demonstrated to be expressed on new vasculature formed in the process of angiogenesis. In rheumatoid arthritis, chronic stimulation of angiogenesis leads to an accumulation of the $\alpha_v\beta_3$ integrin (see U.S. Patent 5,753,230, cited and incorporated by reference on page 45 ln 34 of the instant specification). The presence of the $\alpha_v\beta_3$ integrin stimulates the attachment, adherence and migration of many of the immune cells responsible for the adverse effects involved in RA. The directed targeting of the $\alpha_v\beta_3$ integrin through the use of antagonists, such as the $\alpha_v\beta_3$ specific antibodies of the claimed invention reduces the attachment and recruitment of immune cells. The reduction in the immune cells at the targeted site leads to lowered levels of chronic inflammatory mediators, which are responsible for many of the symptoms of RA. On the other hand, targeting of TNF-α, an inflammatory cytokine with the use of antagonists, namely the TNF-α specific antibody infliximab, works on a very different principle. The model for the use of infliximab is to block the soluble messenger (TNF-α) before the receptor on the target cell is engaged, thereby reducing the signaling events triggering inflammation. This model which involves the systemic treatment of a soluble factor differs greatly from the mechanism that $\alpha_v\beta_3$ specific antibodies employ, which is directly targeted to newly formed vasculature, such as at the site of arthritis.

In addition, the treatment of RA patients with agents such as methotrexate plus TNF-α antagonists results in a high (50%) failure rate (see pg 4 ln 6-9 of the instant specification). The Applicants acknowledged this deficiency in the current standard

of care and, as taught by the specification, recognized that $\alpha_v\beta_3$ antagonists, such as the claimed $\alpha_v\beta_3$ specific antibodies, could potentiate and synergize with certain anti-inflammatory treatments (see pg 4 ln 19-22 of the instant specification). Applicants submit that prior to filing, there were no teachings in the art, much less within the cited references, suggesting combining $\alpha_v\beta_3$ specific antibodies with infliximab to potentiate or synergize the treatment of rheumatoid arthritis.

Applicants respectfully assert that there is no motivation from the primary or secondary references to combine or alter teachings to render the current invention obvious. Secondly, Applicants maintain that, at the time of filing, it would not have been obvious to one skilled in the art to combine $\alpha_v\beta_3$ specific antibodies with infliximab or antigen binding fragments thereof to treat rheumatoid arthritis. Finally, Applicants affirm, as argued above, at the time of filing the teachings of the references in part, or as a whole, do not encompass the scope of using the claimed $\alpha_v\beta_3$ specific antibodies or fragments thereof and infliximab or antigen binding fragments thereof for treating rheumatoid arthritis and therefore fail to support a *prima facie* case of obviousness. Applicants respectfully request that this rejection be withdrawn and not applied to the new claims.

CONCLUSION

Applicants respectfully request that the remarks of the present Response be entered and made of record in the present application. The application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If any additional fees are required in connection with this paper, please charge Deposit Account No. 500479 for the appropriate amount.

Respectfully submitted,

By _____

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